American Journal of Hematology 62:58–60 (1999)

Spontaneous Venous Thrombosis in a Young Patient With Combined Factor V Leiden and Lupus Anticoagulant

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We describe a case of a 28-year-old man who developed an extensive spontaneous deep venous thrombosis. Testing revealed heterozygotic factor V Leiden mutation, and the presence of both lupus anticoagulant (LA) and elevated IgM anticardiolipin antibody (ACA). Several family members were found to be heterozygous for factor V Leiden. A paternal aunt had the factor V Leiden mutation, an elevated plasma homocysteine and a borderline increased IgG ACA level. No other family member had a history of a venous thrombotic event. This case illustrates that evaluation of young patients who present with venous thrombosis should be performed for both hereditary and acquired thrombophilic defects. The family studies suggest that the presence of a lupus anticoagulant may be more clinically significant then elevated ACA in risk assessment. Although screening family members when the proband carries factor V Leiden is controversial, psychological reassurance of those who test negative and simple advice on occupations or social habits (e.g., smoking) for those who test positive may be important benefits. Am. J. Hematol. 62:58–60, 1999. © 1999 Wiley-Liss, Inc.

Key words: factor V Leiden; lupus anticoagulant; venous thrombosis

CASE REPORT

A 28-year-old healthy man developed lower back pain radiating to his buttocks and right leg after lifting a heavy object. This was initially treated with heat and muscle relaxants resulting in a partial relief of symptoms. Two weeks later, his family physician observed that his right leg was swollen. He was advised to go to the emergency room. He had been a cigarette smoker for 10 years. No member of his family or relative were known to have had a thrombotic event. Physical examination was remarkable only for a swollen right leg.

A venous duplex of the right lower extremity showed an acute deep venous thrombosis extending from the calf veins through the popliteal, superficial and common femoral veins and into the external iliac veins. Furthermore, a computed tomography scan of the abdomen revealed an extensive thrombus within the distal inferior vena cava (IVC) immediately proximal to the bifurcation. The thrombus was lyzed with urokinase and a follow-up angiography showed a complete resolution of the thrombus in the iliac vein. However, the IVC was still occluded with large draining collaterals around and a magnetic resonance imaging scan showed an occluded IVC the level of the aortic bifurcation upward to the level of the renal veins.

Investigations were performed for thrombophilia on a sample drawn prior to any treatment (Table I). Abnormal tests were: IgM ACA 71 MPL units (normal < 9); LA-ratio screen 1.4 (normal < 1.2) and activated protein C resistance ratio 1.3 (normal >2.0). Polymerase chain reaction (PCR) analysis showed heterozygosity for factor V Leiden. Intravenous heparin was given for several days and he was subsequently discharged on warfarin to be taken indefinitely. Fifteen months later the swelling of his right leg has resolved and there has been no further venous thromboembolic (VTE) event.

Available family members were similarly screened for thrombophilia (Table I). Several tested positive for factor

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Received for publication 13 November 1998; Accepted 28 May 1999

TABLE I. Laboratory Tests for Thrombophilia

I. Inherited Disorders:
- Antithrombin III
- Protein C
- Free protein S
- Screening for activated protein C resistance; if positive, confirmation by polymerase chain reaction
- Factor II activity; if activity is in higher percentiles, test for prothrombin gene 20210G-A polymorphism
- Total plasma homocysteine

II. Acquired Disorders
- Lupus anticoagulant screen; if positive, confirmation by phospholipid neutralization test
- Anticardiolipin antibody isotypes (IgM, IgG, IgA)

V Leiden, one of whom had in addition a borderline elevated IgG ACA (18 GPL/ml; normal <16) and an elevated homocysteine level (22 μM/L; normal <14 μM/L). Furthermore, a cousin had an elevated IgM ACA (15 MPL/ml; normal < 9) as an isolated abnormal laboratory finding (Fig. 1).

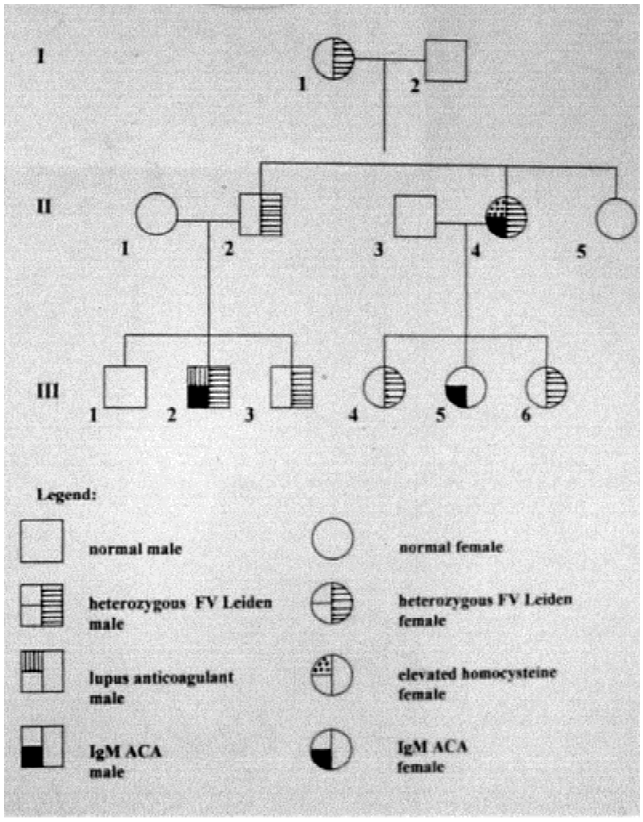

Fig. 1. Laboratory results of screening asymptomatic family members for thrombophilia. The proband is III-2.

DISCUSSION

Thrombophilia is a predisposition to thrombosis which can be inherited or acquired. Antithrombin III, protein C, and protein S deficiencies; and factor V Leiden gene mutation and the prothrombin gene polymorphism 20210G-A are inherited in an autosomal dominant fashion. Among these, factor V Leiden mutation is the most common defect in Caucasians and is present in 20% to 50% of patients with venous thrombosis [1]. On the other hand, lupus anticoagulant and anticardiolipin antibodies are acquired abnormalities predisposing to thrombosis. The odds ratio for the association between LA and venous thromboembolism has been estimated at 9.4 [2]. Conflicting data suggest that elevation of ACA as a single abnormality, particularly IgG isotype, may also increase the risk of VTE [2,3].

Combined defects increase the risk for thrombosis. In a recent series of 110 patients with thrombotic events in whom a predisposing abnormality was established, 16% had combined defects. The most common were ACA and LA, occurring in 8 out of 18 patients [4]. Combined genetic defects appear to act synergistically, increasing the risk of VTE several fold: 73% of family members with combined protein C deficiency and factor V Leiden and 80% of patients with factor V Leiden and protein S deficiency will exhibit a VTE before age 40 [5,6]. Furthermore, co-existing clinical risk factors and the factor V Leiden mutation also increase the risk of thromboembolic events, e.g., oral contraceptives increase the risk 35-fold [7] while tobacco increases the risk of developing myocardial infarction 32-fold [8]. In addition, management of venous thrombosis is influenced by the laboratory findings [9]. It is highly likely that the combined factor V Leiden gene mutation, the presence of a lupus anticoagulant and cigarette smoking, acting in concert, were causally responsible for the massive thrombosis in this patient at his young age.

Family members of affected patient (Fig. 1 III-2) may be considered for screening and many will test positive, as in this case (Fig. 1). Additional findings were the elevated total homocysteine level and IgM ACA in an aunt and the isolated elevated IgM ACA in a cousin. Knowing the presence of combined defects increases the aunt's risk for VTE and could explain clinical events such as recurrent fetal loss, if she were in the childbearing age [10]. Furthermore, the incidence of thromboembolism increases with age in patients with elevated homocysteine levels [11]. Had she been tested for a factor V Leiden only, she would have been inadequately advised regarding the risks of VTE. Although we recognize that screening of asymptomatic family members is controversial [12], our experience in this case was that those family members who tested negative were psychologically reassured and those who tested positive were given advise on occupations (e.g., prolonged driving in a cramped seat), activities (e.g. long airplane trips) or social habits (e.g., smoking) which could put them at increased risk for venous thrombosis.

CONCLUSION

Young patients presenting with venous thrombosis should be fully evaluated for hereditary and acquired thrombophilia risk. Screening of family members should be considered for risk assessment and counseling. The presence of a LA and higher ACA levels may have a greater clinical significance than lower ACA titers and the absence of a LA in exerting a synergistic effect in promoting venous thrombosis.

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